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CORONAVIRUS DISEASE AND IMMUNOTHERAPY IN JUVENILE IDIOPATHIC ARTHRITIS

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The COVID-19 pandemic was a huge challenge to paediatricians around the world. The treatment of patients with juvenile idiopathic arthritis (JIA) and COVID-19 infection could present a potential ethical and medical dilemma. Here we discuss the results of a medical survey made on the parents of children with JIA. Our primary aim was to determine if there was a significant difference in the number of flares of JIA after COVID-19 infection between the group of children who were receiving biological drugs and children not receiving biologicals. Other goals were to investigate the parents' motivation to vaccinate children against SARS-CoV-2 and to determine the most frequent symptoms of COVID-19 infection in these children. A retrospective study was based on the data of a telephone survey conducted between March 10, 2022, and May 12, 2022, including 65 paediatric patients with JIA. The data were provided from the Heliant Health information system database. In children who tested positive for SARS-CoV-2, the most frequent symptom was fever, followed by upper respiratory symptoms. Four flares of JIA were observed in the group of children on biological therapy, while in the group without biologicals two flares followed the COVID-19 infection. The parents' motivation for vaccination against SARS-CoV-2 was extremely low. Our survey-based research did not find a significant difference regarding the COVID-19 infection between children with JIA on biologicals and children with JIA not receiving biologicals, but it did emphasise the parents' hesitancy about vaccination. We propose building a unique database for patients with the diagnosis of JIA which could improve the quality of life of these patients.

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Key words: *coronavirus disease, juvenile idiopathic arthritis, severe acute respiratory syndrome coronavirus 2, flare, biologicals*

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Introduction

The start of the coronavirus disease (COVID-19) pandemic was announced on March 11, 2020 by the World Health Organization (WHO). From that moment, until writing the introductory part of this article, it was estimated that the disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) took approximately 20 million lives (1), thus leaving deep and unfathomable consequences on society, medicine, economy, however, it also contributed to the development of various sociological and cultural phenomena. SARS-CoV-2 is an infective agent constituted of nucleocapsid, membrane, envelope, and spike (S) protein. It is characterized by a high transmission efficacy and genetic similarity to SARS and MERS viruses. The spike protein engages with ACE-2 receptors of human cells, which allows the entry of a virus particle in the cell (2–5). Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children. Its aetiology is still unknown, although it is thought to be provoked by a complex interaction between genetic and environmental factors such as infections, human leukocyte antigen (HLA), gut microbiota, etc. It is classified by the International League of Associations for Rheumatology (ILAR) into several subtypes (6–9). Due to its pathophysiology, it is considered a polygenic autoinflammatory disease. Disease-modifying antirheumatic drugs (DMARDs) represent a group of drugs used in the treatment of rheumatic diseases in the paediatric and adult populations. A specific mechanism of monoclonal antibodies provides targeted neutralization of certain cytokines involved in the pathogenesis of JIA. These medications can silence the disease course and provide remission periods for patients

with JIA (10, 11). Although interleukin-6, interleukin-1 and tumour necrosis factor inhibitors safety profiles are regarded highly acceptable, their use in patients with JIA, and especially in patients with comorbidities, could provoke an increased risk of infections (12–14). Another aspect of COVID-19 pandemic is dealing with COVID-19 paediatric patients who have comorbidities. Patients with JIA constitute such population. Pfizer-BioNTech COVID-19 vaccine is an mRNA-based vaccine and the only vaccine registered for use in the paediatric population in Serbia. Vaccine hesitancy, mostly caused by misinformation, was a major problem in fighting with COVID-19 pandemic, especially in paediatric patients (15). Potential flares that can be provoked by other infections could possibly occur after COVID-19 infection. Fever that can occur in both COVID-19 and JIA must be carefully evaluated. Other important aspects are when to vaccinate taking into consideration immunosuppressive therapy in JIA patients. Therefore, patients with JIA and COVID-19 infection could present a potential ethical and medical dilemma, and every single case must be closely monitored. Here we discuss the results of a medical survey conducted during pandemics, involving parents whose children were diagnosed with JIA.

Aim

Our primary aim was to determine if there was a significant difference in the number of juvenile idiopathic arthritis flares that could be related to SARS-CoV-2 infection between the group of children with JIA who were receiving biological drugs and children with JIA not receiving biological drugs. Other goals were to investigate the parents' motivation to vaccinate children against SARS-CoV-2 and to determine the most frequent symptoms of COVID-19 infection in this population.

Materials and Methods

A retrospective study based on the data of a telephone survey was conducted between March 10, 2022 and May 12, 2022, and it included 65 paediatric patients diagnosed with juvenile idiopathic arthritis. Parents were beforehand informed to anticipate a call from a physician. The survey referred to the period from the beginning of the pandemic. Children were divided into two groups—one that was receiving monoclonal antibodies as a part of the treatment for JIA (n = 9), and the control group that consisted of children with the diagnosis of JIA, who were not receiving biological drugs. The control group (n = 26) included children who were receiving methotrexate and other DMARDs, but also children in disease remission. Some of the research data considering the total duration of JIA, parent's phone numbers and treatment were provided through the Heliant database. Other data were provided from the survey. The survey contained a series of closed and open-ended questions about COVID-19, to which parents gave answers, and it could be roughly divided into four clusters: 1) Positivity or prolonged contact with household members; 2) Symptoms that predominated infection; 3) Potential flares of JIA that followed the infection; 4) Vaccinal status or parents motivation to vaccinate children against SARS-CoV-2. A Chi-squared test was used for group comparison.

Results

Gender, age, and duration of the disease (JIA) are shown in Table 1. The number of positive tested children or children with JIA in prolonged contact with household members tested positive for COVID-19, a number of flares that followed COVID-19 infection and number of parents who vaccinated or were motivated to vaccinate their children are shown in Table 2, along with the most frequently noted symptoms. Therapy of children on biological drugs was adalimumab (n = 18, 48.6%), etanercept (n = 11, 29.7%) and tocilizumab (n = 8, 21.6%) together with methotrexate. For two cases, the data for the type of biological treatment in the Heliant healthcare information system database were not available.

Table 1. Characteristics of JIA patients

	Biological therapy		Control group		Total
Gender	Male	Female	Male	Female	Male and female
	10(25.64%)	29(74.35%)	11(40.74%)	15(59.25%)	65(100%)
Age	11.75 ± 4.70		9.71 ± 4.61		10.87 ± 4.75
Disease duration*	7.11 ± 10.90†		3.93 ± 2.32†		5.84 ± 8.67

*Total time with the diagnosis of JIA. †Disease duration was unknown for one case on biological therapy and two cases in the control group. The biological therapy group showed a greater variation of data for disease duration.

Table 2. Survey results

	Biological therapy	Control group	Total	Symptoms
Positive / contact*	31 (79.48%)	20 (76.93%)	51 (78.46%)	- Fever - Nasal congestion, rhinorrhoea - Cough, sore throat - Myalgias, fatigue
Flares of JIA†	4 (10.25%)	2 (7.70%)	7 (10.78%)‡	
Motivated / vaccinated	3 (7.69%)	1 (3.84%)	4 (6.15%)	

*Tested positive or in prolonged contact with family or household members who tested positive for COVID-19. †Flares of JIA that followed COVID-19 infection. ‡In one case, exacerbation of JIA did not occur after COVID-19 infection. No significant statistical difference b/w the groups was noted $p > 0.05$.

In the group without biologicals, treatment was methotrexate (n = 14, 53.8%), hydroxychloroquine (n = 2, 7.7%), naproxen with methotrexate (n = 2, 7.7%), naproxen (n = 2, 7.7%), prednisone with methotrexate (n = 1, 3.8%) and physical therapy (n = 5, 19.2%). In one case (n = 1, 3.84%), the disease exacerbation occurred after parents did not show up for regular check-ups during lockdown for about two months. In children that tested positive for SARS-CoV-2 on PCR or antigen test (n = 22), the most frequent symptom was fever (n = 14, 63.6%). Fever was < 39 °C in all cases, except in one where it measured above 39 °C (on one occasion 39.8 °C). Other symptoms noted were upper respiratory symptoms (cough, nasal congestion, sore throat, etc.), fatigue, myalgias and conjunctivitis. Parents of three children noted an asymptomatic infection (n = 3, 14%) that was proven with antibody testing. In most cases, symptoms were mild and mostly lasted less than a week. In one case, parents noted that their child had a loss of smell and taste problems that persisted for almost six months. No significant statistical difference was found in the number of flares that followed COVID-19 infection between children with JIA who were receiving biological drugs and children with the diagnosis of JIA not receiving biological drugs (χ^2 with Yates correction was 0.0077, p = .930299. Not significant at $p < .05$). As a reason for not vaccinating their children or lack of motivation for vaccination, most parents reported a misconception that vaccines were not tested enough and were experimental. Relative risk for flares was R = 1.33 (R > 1) in the group of children receiving biologicals compared to the group of children without biologicals in their treatment.

Discussion

In our survey-based research, we tried to examine whether there was a significant difference in the number of flares that could be related to SARS-CoV-2 infection, between paediatric patients with the diagnosis of JIA who were on biological therapy and paediatric patients with the diagnosis of JIA not receiving these drugs.

Key points:

-Patients with the diagnosis of juvenile idiopathic arthritis (JIA) usually had a mild form of COVID-19 disease.

-There were cases where flares of JIA occurred after the infection with SARS-CoV-2.

-We failed to prove that a greater risk of flares after SARS-CoV-2 infection existed in the group of paediatric patients with JIA who were receiving biological drugs.

-It was evident that parents' motivation to vaccinate their children against SARS-CoV-29 was extremely low.

The course of COVID-19 infection in children is usually milder and more asymptomatic compared to the adult population. The most frequent symptoms noted by authors are fever, cough, and rhinorrhoea, which is consistent with our results (Table 2). Most paediatric patients who required ICU admission had comorbidities such as cancer (16–17). The course of COVID-19 infection in paediatric patients with JIA is generally not much different than the course of infection in the rest of the paediatric population, although the risk of exacerbations of JIA triggered by infection was observed (18). This was also evident in our study. It was noted that COVID-19 infection could provoke flares of JIA in paediatric patients in remission or with inactive disease (19, 20). Increased relapse rate during lockdown was found in one Italian study (18), which could be caused by organization problems and general healthcare management. Nevertheless, the full impact of COVID-19 is still to be investigated for this group of patients. The total number of disease exacerbations observed in our study could also be caused by factors other than COVID-19, not evaluated by the survey (prolonged period off drugs, worsening of disease activity, stress, etc.). We could speculate about a protective effect of

TNF-α blockers against cytokine storm syndrome (CSS) in paediatric patients with JIA who are on TNF-α inhibitors, as this potential effect was described in adult patients with rheumatic disease (21, 22). A small discrepancy between our two groups in the number of flares after COVID-19 (biologicals vs. without biologicals, 4 : 2, with RR = 1.33) could be a consequence of disease severity, however, a larger study is needed to evaluate the true meaning of these data. Patients who require monoclonal antibodies in treatment are more likely to have more serious illnesses and likely more prone to disease exacerbations. Smell and taste dysfunction that lasted for almost six months was noted in one child in our study. Prolonged loss of taste and smell is a symptom described as part of Long COVID (23, 24). Parents of children who were receiving biological drugs talked more freely about COVID-19 vaccination, and there is a slight discrepancy in motivation towards vaccination between the two groups (biologicals vs. without biologicals 3 : 1). This could be caused by frequent contact with healthcare workers. Parents' extremely low motivation for vaccinating their children against COVID-19 can be caused by multiple factors. A significant component of vaccination hesitancy may be conflicting and inadequate media coverage (25, 26). Parents who are vaccinated are more likely to vaccinate their children. The important factor for this decision may be parents' level of education (27, 28). Having in mind that most parents noted as a reason for not vaccinating their children that vaccines were not tested enough and were experimental, an adequate strategy and promotion campaign could present a potential solution to this problem (15, 29).

Conclusion

Our survey-based research did not demonstrate a significant difference in terms of COVID-19 infection-provoked flares between children with JIA who were receiving biological drugs and children with JIA who were not on biologicals, but it did emphasize the problems with parents' trust in vaccines, so similar surveys can be helpful in the future, and on the larger scale they could provide more significant and reliable data. Therefore, we propose building a unique database for paediatric patients with the diagnosis of juvenile idiopathic arthritis, so that healthcare workers dealing with this population could have a better concept of how to provide a better quality of life for their patients.

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COVID-19 I IMUNOTERAPIJA U JUVENILNOM IDIOPATSKOM ARTRITISU

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Pandemija COVID-19 predstavlja ogroman izazov za pedijatre širom sveta. Dece obolele od juvenilnog idiopatskog artritisa (JIA) koja imaju COVID-19 i koja su po indikacijama na biološkoj terapiji može lekare dovesti do medicinske i etičke dileme. Nastojali smo da u ovom radu odgovorimo na pitanje da li je sklonost ka egzacerbacijama JIA nakon preležane infekcije COVID-19 veća kod dece sa JIA na biološkoj terapiji nego kod dece sa JIA koja nisu na biološkoj terapiji. Osim toga, ispitali smo motivaciju roditelja za vakcinaciju dece i simptome bolesti COVID-19 u ovoj populaciji. Retrospektivna studija sprovedena je na osnovu rezultata ankete rađene između 10. 3. 2022. i 12. 5. 2022. godine koja je obuhvatila 65 pedijatrijskih bolesnika. Anketa je sadržala niz zatvorenih i otvorenih pitanja na koja su odgovarali roditelji. Deo podataka koji se ticao trajanja JIA, brojeva telefona i terapije preuzet je iz *Heliant* informacionog sistema. Za poređenje grupa korišćen je Hi-kvadrat test. Pokazalo se da je najčešći simptom bila povišena telesna temperatura, a pratili su je simptomi vezani za gornji respiratorni trakt. Egzacerbacija osnovne bolesti koja je usledila nakon COVID-19 infekcije u grupi dece na biološkoj terapiji sa JIA potvrđena je u četiri slučaja, dok je u grupi dece sa JIA koja nisu bila na biološkoj terapiji pogoršanje zabeleženo dva puta. Prilikom poređenja dveju pomenutih grupa nije nađeno statistički značajno odstupanje. Motivacija roditelja za vakcinaciju protiv SARS-CoV-2 bila je izuzetno niska. Studija koja bi obuhvatila veći broj obolelih od JIA dala bi pouzdanije podatke o uticaju COVID-19 na ovu grupu bolesnika. Predlaže se formiranje jedinstvene baze podataka dece sa JIA, budući da bi ona u budućnosti mogla pomoći kliničarima da poboljšaju kvalitet života ovih bolesnika.

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***Ključne reči**: bolest izazvana koronavirusom, juvenilni idiopatski artritis, severe acute respiratory syndrome coronavirus 2, biološka terapija, egzacerbacija*